Vaccines Immunoglobulins and Antisera

The agents described in this section are immunological agents used for both active and passive immunisation.

Active immunisation is the exposure of the immune system to antigens in the form of micro-organisms or products of their activity in order to stimulate production of antibodies and acquired cell-mediated responses with a specific protective capacity. It may be a natural process after infection, or an artificial process induced by giving *vaccines*. It is inevitably a slow process dependent upon the rate at which the antibodies can be produced. Although the terms vaccination and immunisation are often used synonymously and interchangeably, *vaccination* simply refers to giving a vaccine whereas *immunisation* implies the development of protective levels of antibodies.

Passive immunisation, which results in immediate short-term protection, may be achieved by giving exogenous antibodies in the form of *antisera* (of animal origin) or *immunoglobulins*.

Antisera

Antisérums; Antisueros; Immunsera.

Антисыворотки

Description

Antisera (immunosera) are sterile preparations containing immunoglobulins obtained from the serum of immunised animals by purification. The term antisera includes antitoxins, which are antibodies that combine with and neutralise specific toxins, and antivenins (antivenoms), which are antitoxins directed against the toxic principle of the venoms of poisonous animals such as certain snakes and arthropods.

Antisera are obtained from healthy animals immunised by injections of the appropriate toxins or toxoids, venins, or suspensions of micro-organisms or other antigens. The specific immunoglobulins may be obtained from the serum by fractional precipitation and enzyme treatment or by other chemical or physical means. A suitable antimicrobial preservative may be added, and is invariably added if the product is issued in multidose containers. The Ph. Eur. 6.2 directs that when antisera contain phenol, the concentration is not more than 0.25%. The antiserum is distributed aseptically into sterile containers, which are sealed so as to exclude micro-organisms. Alternatively they may be supplied as freeze-dried preparations for reconstitution immediately before use.

Adverse Effects and Precautions

Reactions are liable to occur after the injection of any serum of animal origin. Anaphylaxis (type I hypersensitivity reaction, p.561) may occur, with hypotension, dyspnoea, urticaria, and shock, which requires management as a medical emergency (see p.1205).

Serum sickness (type III hypersensitivity reaction, p.561) may also occur, frequently 7 to 10 days after the injection of serum of animal origin.

Before injecting serum, information should be obtained whenever possible as to whether the patient is subject to hypersensitivity disorders or has received serum injections before. Sensitivity testing should be performed before giving antisera. The patient must be kept under observation after giving a full dose of antisera. Adrenaline injection and resuscitation facilities should be available.

Uses and Administration

Antisera have the specific power of neutralising venoms or bacterial toxins, or combining with the bacterium, virus, or other antigen used for their preparation. Most antisera in current use are antitoxins or antivenins. The use of antisera to induce passive immunity has declined; immunoglobulins are preferred. Although antisera are defined as being of animal origin (see above), the term antisera has been used in some countries to describe antitoxins of human origin (immunoglobulins).

Immunoglobulins

Immunglobuline; Inmunoglobulinas.

Иммуноглобулины

Description

Immunoglobulins are produced by B lymphocytes as part of the humoral response to foreign antigens. Immunoglobulins used in clinical practice are preparations containing antibodies, usually prepared from human plasma or serum, and mainly comprise IgG. Normal immunoglobulin, prepared from material from blood donors, contains several antibodies against infectious diseases prevalent in the general population, whereas specific immunoglobulins contain minimum specified levels of one antibody. Antibodies may also be prepared by genetic engineering techniques.

Adverse Effects

Local reactions with pain and tenderness at the site of intramuscular injection may follow the use of immunoglobulins. Hypersensitivity reactions, including, rarely, anaphylactic reactions, have also been reported; such reactions, though, are far less frequent than after the use of antisera of animal origin.

Some immunoglobulins are available as intravenous preparations. Systemic reactions with fever, chills, facial flushing, headache, and nausea may occur, particularly at high rates of infusion.

Precautions

Strenuous efforts are made to screen human donor material used in the preparation of immunoglobulins; the transmission of infections, including hepatitis B and HIV, which has been associated with the use of certain blood products (see p.1056), does not appear to be a problem with the immunoglobulins currently in use.

IgA, present in some immunoglobulin preparations, may give rise to the production of anti-IgA antibodies in patients with IgA deficiencies, with the consequent risk of anaphylactic reactions. For precautions in such patients, see Hypersensitivity under Adverse Effects and Precautions in Normal Immunoglobulins, p.2226.

Interactions

Immunoglobulins may interfere with the ability of live vaccines to induce an immune response and a suitable interval should separate their use (see Vaccines, Interactions, p.2202).

Uses and Administration

Immunoglobulins are used for passive immunisation, thus conferring immediate protection against some infectious diseases. They are preferred to antisera of animal origin as the incidence of adverse reactions is lower.

It is generally important to follow the conferment of passive immunity, which is largely an emergency procedure, by the injection of suitable antigens to produce active immunity.

Vaccines

Vacunas.

Вакцины

Description

Vaccines are traditionally preparations of antigenic materials that are given with the objective of inducing in the recipient active immunity to specific infecting agents or toxins or antigens produced by them. They may contain living or killed micro-organisms, bacterial toxoids, or antigenic material from particular parts of the infecting organism, which may be derived from the organism or produced by recombinant DNA technology. Vaccines may be single-component vaccines or mixed combined vaccines. Vaccines against some non-infectious diseases are being developed.

Storage. All vaccines are sensitive to heat to differing extents, with oral poliomyelitis vaccines and measles vaccines the most heat-sensitive of the commonly used vaccines. Freeze-dried vaccines become much more heat-sensitive once reconstituted. The effect of heat on vaccines is generally irreversible loss of potency, but in some cases heat exposure may also cause the vaccine to become more reactogenic. The system used for storing and distributing vaccines at sufficiently low temperature is called the cold chain, and consists of a series of storage and transport links all designed to keep the vaccine at the correct temperature until it reaches the user. WHO recommends[1] that oral poliomyelitis vaccines be stored at −25 to −15° and that, in general, freeze-dried vaccines should be stored at 2 to 8°.

Some vaccines are also sensitive to excessive cold, notably hepatitis B vaccines and Haemophilus influenzae vaccines, and care should be taken not to store them at too low a temperature.[1]

In addition to temperature sensitivity, some vaccines are also sensitive to strong light, such as BCG vaccines, measles-containing vaccines, and rubella-containing vaccines. These are usually supplied in dark brown glass vials for protection, but further care should be taken to keep them covered.[1]

Further advice concerning vaccine storage is given in the references below.[2-6]

1. WHO. What are the correct conditions for storing EPI vaccines? Available at: http://www.who.int/vaccines-access/vacman/temperature/temperature.htm (accessed 26/09/05)
2. Galazka A, *et al.*: Global Programme for Vaccines and Immunization. *Thermostability of vaccines.* Geneva: WHO, 1998. Also available at: http://whqlibdoc.who.int/hq/1998/WHO_GPV_98.07.pdf (accessed 14/07/08)
3. Department of Vaccines and Other Biologicals. *Temperature monitors for vaccines and the cold chain.* Geneva: WHO, 1999. Also available at: http://www.who.int/vaccines-documents/DocsPDF/www9804.pdf (accessed 15/09/05)
4. CDC. Notice to readers: guidelines for maintaining and managing the vaccine cold chain. *MMWR* 2003; **52:** 1023–5. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5242.pdf (accessed 24/05/06)
5. Australian Government Department of Health and Ageing. National vaccine storage guidelines: strive for 5 (2005). Available at: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/5B7381C34C511E54CA25719D00183397/06.00File/strive-4-five.pdf (accessed 14/07/08)
6. Public Health Agency of Canada. National vaccine storage and handling guidelines for immunization providers (2007). Available at: http://www.phac-aspc.gc.ca/publicat/2007/nvshglp-ldemv/index-eng.php (accessed 05/06/08)

Adverse Effects

Injection of a vaccine may be followed by a local reaction, possibly with inflammation and lymphangitis. An induration or sterile abscess may develop at the injection site. Fever, headache, and malaise may start a few hours after injection and last for 1 or 2 days. Hypersensitivity reactions may occur and anaphylaxis has been reported rarely.

Further details, if appropriate, of adverse effects of vaccines may be found in the respective individual monographs.

Anaphylaxis. In a retrospective study[1] in the USA conducted to quantify the risk of anaphylaxis after vaccination of children and adolescents, only 5 cases potentially associated with vaccines were identified from more than 7.5 million doses given. Vaccines implicated were generally given in combination and included the following components: diphtheria and tetanus; diphtheria, tetanus, and pertussis; hepatitis B; Haemophilus influenzae; measles, mumps, and rubella; and oral poliomyelitis. One case followed measles, mumps, and rubella vaccine given alone. It was concluded that vaccine-associated anaphylaxis is a rare event.

1. Bohlke K, *et al.* Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; **112:** 815–20.

Long-term effects. The introduction of routine childhood vaccination has been accompanied by concerns over the safety and possible long term sequelae of some commonly used vaccines. Difficulties have arisen in distinguishing temporal and causal associations and in some cases the perceived dangers of vaccination have impeded uptake. Among the disorders that have been temporally (but generally not causally) associated with childhood vaccination are neurological disorders, sudden infant death syndrome, type 1 diabetes mellitus, and demyelinating disorders. Information on adverse effects associated with specific vaccines can be found under diphtheria, tetanus, and pertussis vaccines (p.2210), hepatitis B vaccines (p.2215), influenza vaccines (p.2218), measles, mumps, and rubella vaccines (p.2223), and pertussis vaccines (p.2230).

Additives or excipients have sometimes been alleged to be the cause of adverse reactions—see below for further details.

References.

1. Jefferson T. Vaccination and its adverse effects: real or perceived. *BMJ* 1998; **317:** 159–60.
2. Ball LK, *et al.* Risky business: challenges in vaccine risk communication. *Pediatrics* 1998; **101:** 453–8.
3. Hiltunen M, *et al.* Immunisation and type 1 diabetes mellitus: is there a link? *Drug Safety* 1999; **20:** 207–12.

4. Institute for Vaccine Safety Diabetes Workshop Panel. Childhood immunizations and type 1 diabetes: summary of an Institute for Vaccine Safety workshop. *Pediatr Infect Dis J* 1999; **18:** 217–22.
5. Stratton K *et al. Immunization safety review: multiple immunizations and immune dysfunction*. Washington DC: National Academy Press, 2002. Also available at: http://www.nap.edu/catalog.php?record_id=10306 (accessed 14/07/08)
6. Offitt PA, Hackett CJ. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics* 2003; **111:** 653–9.
7. Wraith DC, *et al.* Vaccination and autoimmune disease: what is the evidence? *Lancet* 2003; **362:** 1659–66.
8. Stratton K *et al. Immunization safety review: vaccinations and sudden unexpected death in infancy.* Washington DC: National Academy Press, 2003. Also available at: http://www.nap.edu/catalog.php?record_id=10649 (accessed 14/07/08)
9. CDC. Surveillance for safety after immunization: vaccine adverse event reporting system (VAERS) — United States, 1991–2001. *MMWR* 2003; **52** (SS-1): 1–24. Correction. *ibid.*; 113.
10. Hviid A, *et al.* Childhood vaccination and type 1 diabetes. *N Engl J Med* 2004; **350:** 1398–1404.
11. Koppen S, *et al.* No epidemiological evidence for infant vaccination to cause allergic disease. *Vaccine* 2004; **22:** 3375–85.
12. Schattner A. Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. *Vaccine* 2005; **23:** 3876–86.

Effects of adjuvants. *Aluminium hydroxide* has been used frequently as an adsorbent in vaccines. A review[1] found significantly more erythema and induration with aluminium-containing vaccines than with plain ones. There was, however, no evidence of serious or long-lasting adverse effects that could be attributed to aluminium salts.

Thiomersal has been used as a preservative but because of alleged adverse effects is no longer used as widely as it once was (see Vaccines, under Thiomersal, p.1664 for further details). However, the comment has been made that in developing countries far more benefit will be seen from protecting children with current, inexpensive, domestically-manufactured thiomersal-containing vaccines, than by investing in thiomersal-free alternatives.[2]

1. Jefferson T, *et al* Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. *Lancet Infect Dis* 2004: **4:** 84–90.
2. Bigham M, Copes R. Thiomersal in vaccines: balancing the risk of adverse effects with the risk of vaccine-preventable disease. *Drug Safety* 2005; **28:** 89–101.

Effects on the nervous system. ***GUILLAIN-BARRÉ SYNDROME.*** Guillain-Barré syndrome (see p.2228) has occasionally been reported after vaccination, although causal relationships have been difficult to evaluate. Such reports have been made after diphtheria and tetanus vaccines (p.2210), haemophilus influenzae vaccines (p.2213), hepatitis A vaccines (p.2214), hepatitis B vaccines (p.2215), a swine influenza vaccine (p.2218), measles, mumps, and rubella vaccines (p.2223), meningococcal vaccines (p.2224), and oral poliomyelitis vaccines (p.2232), although only the association with swine influenza vaccine appears to have been accepted.

Precautions

Most persons can safely receive the majority of vaccines. In a few individuals vaccination is contra-indicated or should be deferred.

All vaccines are contra-indicated in those who have had a previous confirmed anaphylactic reaction to a previous dose of a vaccine containing the same antigens or a confirmed anaphylactic reaction to another component contained in the relevant vaccine (for example, neomycin, polymyxin B, or streptomycin which may be present in trace amounts).

Some vaccines are prepared in egg cultures and are contra-indicated in persons with a confirmed anaphylactic reaction to egg.

Live vaccines are contra-indicated in the following groups of immunosuppressed patients:

- severe primary immunodeficiency
- malignant disease being treated with either chemotherapy or radiotherapy and for at least 6 months after stopping such treatment
- solid organ transplant receiving immunosuppressive therapy
- bone marrow transplant and for at least 12 months after stopping immunosuppressive therapy (or longer if graft-versus-host disease develops)
- all patients receiving high-dose systemic corticosteroids until at least 3 months after stopping treatment; this includes children receiving prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2 mg/kg for at least 1 week or 1 mg/kg for 1 month and adults receiving a daily dose of 40 mg for more than 1 week.
- HIV positive patients with immunosuppression

Vaccination may be delayed in persons who are acutely unwell and in those with evolving neurological conditions (until stabilised). In pregnancy, vaccination should be delayed until after delivery; termination of pregnancy is not recommended if a vaccine is inadvertently given during pregnancy.

If any alcohol or disinfectant is used for cleansing the skin it should be allowed to evaporate before vaccination otherwise inactivation of live vaccines may occur.

Immunocompromised patients. For a discussion of the use of vaccines in HIV-infected and otherwise immunocompromised patients, see under Uses, below.

Premature infants. In the UK, the Royal College of Paediatrics and Child Health[1] and the Department of Health[2] consider that all routine childhood immunisations should be scheduled on the basis of the child's actual date of birth with no allowance being made for prematurity. In the USA, the American Academy of Pediatrics offers similar advice.[3] It is acknowledged that more studies are required into immunisation in prematurity, particularly in infants receiving corticosteroids.[1] There is some evidence that a minority of premature infants may fail to respond adequately to Haemophilus influenzae vaccines and to hepatitis B immunisation.[1]

1. Royal College of Paediatrics and Child Health. Immunisation of the immunocompromised child: best practice statement February 2002. Available at: http://www.rcpch.ac.uk/Publications/Publications-list-by-title (accessed 14/07/08)
2. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book" Available at: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX (accessed 26/04/06)
3. Pickering L, *et al.* eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2006.

Interactions

The ability of vaccines to induce an immune response can be influenced by the recent use of other vaccines or immunoglobulins. Live vaccines should either be given simultaneously (but at different sites) or an interval of at least 3 weeks allowed between them. Live vaccines should normally be given at least 3 weeks before or at least 3 months after the use of immunoglobulin. However, travellers should receive appropriate vaccines regardless of these limitations if time is short.

Patients receiving immunosuppressant therapy, including antineoplastics or therapeutic doses of corticosteroids, may also display a reduced response to vaccines and deferral of immunisation is advised, see Precautions, above. For further details on immunisation in immunocompromised patients, see under Uses and Administration, below.

Any agent that is active against the bacterial or viral strain present in the vaccine may interfere with development of a protective immune response but treatment with antibacterials is not a contra-indication to immunisation.

Uses and Administration

Vaccines are used for active immunisation as a prophylactic measure against some infectious diseases. They provide partial or complete protection for months or years. For inactivated vaccines, a slight and rather slow antibody response of primarily immunoglobulin M (IgM) (the primary response) is produced after the first or second dose but, when a further dose is given after a suitable interval, a prompt antibody response follows and high concentrations of IgG occur in the blood (the secondary response). Though the antibody concentration may later fall, a further dose of vaccine promptly restores it. For most live vaccines only one dose is required, although 3 doses of live (oral) poliomyelitis vaccines are needed to achieve complete immunisation. Some inactivated vaccines contain an adjuvant such as aluminium hydroxide or aluminium phosphate to enhance the immune response.

Protection against several infectious diseases may be provided in early life by active immunisation and national schedules for childhood immunisation are regularly reviewed and updated. Schedules for routine immunisation of infants and children are generally designed to fit in with routine health checks and landmark events such as school starting and leaving ages. National immunisation schedules should be consulted for full details of local recommendations.

In the **UK**, the following schedule of vaccination and immunisation is recommended:

- at 2 months of age, the first dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine (p.2212), together with a first dose of pneumococcal conjugate vaccine (p.2231)
- at 3 months of age, a second dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine, together with the first dose of meningococcal C conjugate vaccine (p.2224)
- at 4 months of age, a third dose of a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and *Haemophilus influenzae* vaccine, together with a second dose of meningococcal C conjugate vaccine and pneumococcal conjugate vaccine
- at 12 months of age, a fourth dose of *Haemophilus influenzae* vaccine (p.2213) and a third dose of a meningococcal C conjugate vaccine
- at about 13 months, measles, mumps, and rubella vaccine (p.2223) and a third dose of pneumococcal conjugate vaccine
- at 3 years 4 months to 5 years, a reinforcing dose of a combined diphtheria, tetanus, pertussis (acellular component), and poliomyelitis (inactivated) vaccine (p.2211) and a second dose of measles, mumps, and rubella vaccine
- at 12 to 13 years of age, human papillomavirus vaccine (p.2217) will be offered to all girls (starting in September 2008)
- before leaving school (age 13 to 18 years), a reinforcing dose of a low-dose diphtheria, tetanus, and poliomyelitis (inactivated) vaccine (p.2212).

The following schedule is recommended in the **USA**:

- at birth, the first dose of hepatitis B vaccine (p.2215)
- at age 1 to 2 months, a second dose of hepatitis B vaccine, not less than 1 month after the first
- at 2 months, a first dose of diphtheria, tetanus, and pertussis (acellular component) vaccine (p.2210), together with a *Haemophilus influenzae* vaccine (p.2213), a pneumococcal conjugate vaccine (p.2231), a poliomyelitis (inactivated) vaccine (p.2232) and a rotavirus vaccine (p.2236)
- at 4 months, a second dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, together with the second doses of a *Haemophilus influenzae* vaccine, pneumococcal conjugate vaccine, poliomyelitis (inactivated) vaccine, and rotavirus vaccine
- at 6 months, the third dose of *Haemophilus influenzae* vaccine if necessary (depending on the type of vaccine used), a third dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, a third dose of pneumococcal conjugate vaccine and a third dose of rotavirus vaccine
- at 6 to 18 months, the third doses of hepatitis B and poliomyelitis (inactivated) vaccines
- from 6 months to 18 years, annual influenza vaccine in high-risk patients, although influenza vaccine is also recommended in healthy infants aged 6 to 59 months
- from 12 months, 2 doses (at least 6 months apart) of a hepatitis A vaccine (p.2214)
- at 12 to 15 months, a reinforcing dose of *Haemophilus influenzae* vaccine, the first dose of measles, mumps, and rubella vaccine, the first dose of varicella-zoster vaccine (p.2242) and the fourth dose of pneumococcal conjugate vaccine
- at 15 to 18 months, the fourth dose of diphtheria, tetanus, and pertussis (acellular component) vaccine
- at 2 to 18 years, pneumococcal polysaccharide vaccine (in addition to previously administered pneumococcal conjugate vaccine) in certain high-risk groups
- at 2 to 10 years, meningococcal C conjugate vaccine (p.2224) to children with terminal complement deficiencies or asplenia and other high-risk groups; meningococcal polysaccharide vaccine may alternatively be used
- at 4 to 6 years, the fifth dose of diphtheria, tetanus, and pertussis (acellular component) vaccine, the fourth dose of poliomyelitis (inactivated) vaccine, the second dose of measles, mumps, and rubella vaccine, and the second dose of varicella-zoster vaccine

- 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