Normal immunoglobulins. Although the use of live vaccines and immunoglobulins at the same time is generally not recommended, normal immunoglobulin had no effect on the antibody response to oral poliomyelitis vaccine when the 2 preparations were given together to 50 subjects.[1]

1. Green MS, *et al.* Response to trivalent oral poliovirus vaccine with and without immune serum globulin in young adults in Israel in 1988. *J Infect Dis* 1990; **162:** 971–4.

Uses and Administration

Poliomyelitis vaccines are used for active immunisation against poliomyelitis. For discussion of immunisation schedules, see under Vaccines, p.2202. Both live (oral) poliomyelitis vaccines and inactivated poliomyelitis vaccines are available. The oral vaccine stimulates the formation of antibodies both in the blood and in the mucosal tissues of the gastrointestinal tract.

In the UK, an inactivated poliomyelitis vaccine containing the 3 types of poliovirus (trivalent) is recommended for the primary immunisation of all age groups, given as a course of 3 doses at intervals of 4 weeks. It is given intramuscularly as a combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated), and Haemophilus influenzae vaccine. For children who received primary immunisation during infancy, reinforcing doses are recommended at school entry (diphtheria, tetanus, pertussis, and poliomyelitis) and before leaving school (diphtheria, tetanus, and poliomyelitis). Further reinforcing doses are necessary only in adults exposed to infection including travellers to countries where poliomyelitis is epidemic or endemic and healthcare workers in contact with poliomyelitis cases. A single dose is given, repeated every 10 years if necessary.

In the USA, the recommended schedule consists of four doses of inactivated vaccine given at 2 months, 4 months, 6 to 18 months, and 4 to 6 years of age.

On the occurrence of a single case of paralytic poliomyelitis from wild virus, a single dose of the oral vaccine is recommended for all persons in the neighbourhood, regardless of whether they have previously been immunised. A primary course should be completed in previously unimmunised individuals.

Choice of vaccine. Two types of poliomyelitis vaccine are available: live attenuated oral poliomyelitis vaccine (OPV) and inactivated (killed) poliomyelitis vaccine (IPV) given by injection. Both vaccines are highly effective against all 3 types of poliovirus but there are advantages and disadvantages associated with their use.

The *advantages* of OPV are:

- it produces an immune response in both the blood and in the lining of the gut, thus preventing both spread of infection to the CNS and multiplication of the virus in the gastrointestinal tract and hence transmission via the stools and saliva
- it is given orally and is therefore easy to give without specialist training
- it is relatively inexpensive, an important consideration in developing countries in particular.

The *disadvantage* of OPV is:

- it causes very rare cases of vaccine-associated paralytic poliomyelitis (VAPP).

The *advantage* of IPV is:

- it is not a live vaccine and as such carries no risk of VAPP.

The *disadvantages* of IPV are:

- it confers very little immunity in the gastrointestinal tract, hence when an individual immunised with IPV is infected with wild poliovirus the virus can still multiply in the intestines and be shed in the stools, thus risking continued transmission
- trained health workers are required to give it by injection
- it costs far more than OPV.

Poliomyelitis has now been eradicated from most countries in the world (see below) and hence many, including the UK and the USA, consider it appropriate to use IPV exclusively for routine immunisation. However, the Global Polio Eradication Initiative will continue to use OPV where necessary until global eradication is achieved, at which time it has stated that the use of OPV should cease as soon as possible while population immunity against poliomyelitis and surveillance sensitivity for paralysis remain high, and be replaced by routine use of IPV.[1]

1. WHO. Framework for national policy makers in OPV-using countries: cessation of routine oral polio vaccine (OPV) use after global polio eradication. Geneva: WHO, 2005. Also available at: http://www.polioeradication.org/content/publications/OPVCessationFrameworkEnglish.pdf (accessed 12/10/05)

Eradication of infection. In 1988, WHO announced the goal of eradicating poliomyelitis by the year 2000. Other bodies joined the project which became known as the Global Polio Eradication Initiative.[1] Although the goal was not achieved in 2000, very considerable progress has been made. In 1988, wild poliovirus was endemic in 125 countries and more than 1000 children became paralysed every day. In 2005, only 4 countries still had endemic poliomyelitis. However, some countries are experiencing re-infection (11 by the end of August 2005) and in 2005, for the first time, case numbers were higher in these re-infected countries than in those where the disease is endemic. This illustrates the vulnerability of countries considered free of poliomyelitis when resultant low routine immunisation coverage puts children at risk. The global incidence of polio remained unchanged from 2005 to 2006.[2] A renewed goal was set of global polio eradication by the year 2008.

1. Global Polio Eradication Initiative. Information available at: http://www.polioeradication.org (accessed 25/04/06)
2. CDC. Progress towards interruption of wild poliovirus transmission—worldwide, January 2006–May 2007. *MMWR* 2007; **56:** 682–5. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5627a3.htm (accessed 15/04/08)

Preparations

Ph. Eur.: Poliomyelitis Vaccine (Inactivated); Poliomyelitis Vaccine (Oral); ***USP 31:*** Poliovirus Vaccine Inactivated.

Proprietary Preparations (details are given in Part 3)
Arg.: Imovax Polio; Sabin; ***Austral.:*** Enpovax HDC†; Ipol; ***Belg.:*** Imovax Polio; Sabin†; ***Braz.:*** Imovax Polio†; IPV; Vacina Poliomielitica†; ***Cz.:*** Imovax Polio; IPV-Virelon; ***Fin.:*** Imovax Polio; ***Fr.:*** Imovax Polio; ***Ger.:*** IPV Merieux; IPV-Virelon; ***Gr.:*** Imovax Polio†; Poliorix; Vaccine Antipoliomyelitique/Merieux†; ***Hong Kong:*** Imovax Polio; ***Indon.:*** Imovax Polio; ***Israel:*** Imovax Polio; Polio Sabin; Polioral; ***Ital.:*** Imovax Polio; Polio Sabin†; Poliral†; Poliovax-IN; ***Malaysia:*** Polioral†; ***Mex.:*** Polio Sabin; Polioral; ***Norw.:*** Imovax Polio; ***NZ:*** Imovax Polio; Ipol; ***Philipp.:*** Polio Sabin; Polioral; Poliorix; ***Pol.:*** Imovax Polio; Polio Sabin; ***S.Afr.:*** OPV-Merieux; Polioral; ***Singapore:*** Imovax Polio†; ***Spain:*** Vac Antipolio Or†; Vac Polio Sabin; Vac Poliomielitica; ***Swed.:*** Imovax Polio; ***Switz.:*** Poliorix; ***Thai.:*** Polio Sabin; Polioral; ***Turk.:*** Buccapol; Polio Sabin; Poliorix; ***USA:*** Ipol; ***Venez.:*** Imovax Polio†; Vacuna Sabin†.

Pseudomonas Vaccines

Vacunas de pseudomonas.

Profile

A number of candidate *Pseudomonas aeruginosa* vaccines are under investigation for the prevention of pseudomonal infections in a variety of disease states.

◊ *Pseudomonas aeruginosa* is notably resistant to many antibacterials and there has consequently been considerable interest in developing an effective vaccine against it.[1-4] However, clinical results have tended to be disappointing, and together with improvements in antibacterial management have meant that no such vaccine is yet available for clinical use.

Early attempts in the 1960s at developing a vaccine focused on cell wall components (lipopolysaccharides). Multivalent lipopolysaccharide vaccines were tested in *animals* and in patients, including burns patients and patients with various forms of cancer and acute and chronic lung disease but, despite some positive results, these vaccines never gained clinical acceptance because of problems associated with the use of lipopolysaccharides. Vaccines designed at targeting the toxic exoproduct of *Ps. aeruginosa*, exotoxin A, produced mixed results at best; there has also been interest in exotoxin A toxoid in combination with other protective immunogens and in multicomponent and conjugate vaccines. There was brief interest in ribosomes and ribosomal RNA vaccines but these fell out of favour.

The discovery that motility was associated with *Ps. aeruginosa* virulence prompted research into the use of flagella as protective immunogens. The organism normally has two types of flagellum and a divalent vaccine has been tested, but with only modest benefit. There has also been some interest in development of vaccines against pili, bacterial appendages used for attachment.

Some investigators tried the use of high-molecular-weight polysaccharides as potential vaccine candidates but interest in this area has declined. Another defunct area of research is the use of pseudomonal alginate and mucoid exopolysaccharide; these were suggested for use in cystic fibrosis patients but did not progress beyond *animal* studies.

From the 1980s, there was considerable interest in the use of a variety of outer membrane proteins to develop a vaccine, partly because outer membrane proteins are exposed on the cell surface and at least one, protein F, is common to all serotypes. Encouraging results were obtained in *animal* models of infected burns and of chronic lung disease. Preliminary studies in healthy humans yielded large and sustained increases in antibody titres and found outer membrane proteins to be well tolerated. Multicomponent vaccines have been developed consisting of toxoids of known pseudomonal virulence factors such as proteases, elastases, and exotoxin A. Conjugate vaccines have been shown to be effective in *animal* models and to elicit a high antibody titre in cystic fibrosis patients.

In recent years, attention has also turned to the development of DNA vaccines, and to the use of some novel immunological approaches such as the use of pooled monoclonal antibodies directed against a variety of *Ps. aeruginosa* virulence antigens and of epitopes of pseudomonal elastase. In addition, research has shown that both active and passive immunisation with the purified type III translocation protein (PcrV) from *Ps. aeruginosa* is effective in *mouse* models of lung infection and burns, although results of combined active and passive immunisation in clinical studies were disappointing. Finally, there has been interest in obtaining immunological protection by presenting *Pseudomonas* antigens via mucous membranes, particularly in the gastrointestinal tract or intranasally.

1. Keogan MT, Johansen HK. Vaccines for preventing infection with Pseudomonas aeruginosa in people with cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 03/06/05).
2. Cachia PJ, Hodges RS. Synthetic peptide vaccine and antibody therapeutic development: prevention and treatment of Pseudomonas aeruginosa. *Biopolymers* 2003; **71:** 141–68.
3. Holder IA. Pseudomonas vaccination: a historical overview. *Vaccine* 2004; **22:** 831–9.
4. Döring G, Pier GB. Vaccines and immunotherapy against Pseudomonas aeruginosa. *Vaccine* 2008; **26:** 1011–24.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Psaeva†; ***Pol.:*** Pseudovac.

Q Fever Vaccines

Vacunas de la fiebre Q.

Profile

A Q fever vaccine consisting of a purified killed suspension of *Coxiella burnetii* is available in Australia. It is prepared from Phase I Henzerling strain of *C. burnetii* grown in the yolk sacs of embryonated eggs. A single 0.5-mL subcutaneous dose is given for active immunisation in individuals at high risk of Q fever. These include abattoir workers, veterinarians, farmers and others exposed to farm animals, and laboratory workers handling potentially infected tissue.

Before immunisation, patients should be tested for their serum antibody titre and a skin test performed; giving the vaccine to persons already sensitised to Q fever antigens may cause serious hypersensitivity reactions.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Q-Vax.

Rabies Antisera

Antisuero de la rabia.
ATC — J06AA06.

Profile

Rabies antisera have been used to provide passive immunisation against rabies but the use of rabies immunoglobulins (see below) is preferred.

Rabies Immunoglobulins

Inmunoglobulinas contra la rabia.
ATC — J06BB05.

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

Ph. Eur. 6.2 (Human Rabies Immunoglobulin; Immunoglobulinum Humanum Rabicum). A liquid or freeze-dried preparation containing human immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma from donors immunised against rabies and contains specific antibodies that neutralise the rabies virus. Normal immunoglobulin may be added. It contains not less than 150 international units/mL. The liquid preparation should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored, protected from light, in a colourless, glass container, under vacuum or under an inert gas.

USP 31 (Rabies Immune Globulin). A sterile solution of globulins derived from plasma or serum from selected adult human donors who have been immunised with rabies vaccine and have developed high titres of rabies antibody. It contains 10 to 18% of protein of which not less than 80% is monomeric immunoglobulin G. It has a potency of 150 international units/mL. It contains glycine as a stabilising agent, and a suitable preservative. A solution diluted to contain 1% of protein has a pH of 6.4 to 7.2. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Uses and Administration

Rabies immunoglobulins are used for passive immunisation against rabies. They are combined with active immunisation by rabies vaccines (see below) in postexposure treatment for the prevention of rabies in previously unimmunised persons who have been bitten by rabid animals or animals suspected of being rabid. There are 2 types of immunoglobulin available: human rabies immunoglobulin (HRIG) and pepsin-digested or highly purified equine rabies immunoglobulin (ERIG). The recommended dose of HRIG is 20 international units/kg; for ERIG products it is 40 international units/kg. The recommended dose should be infiltrated in and around the cleansed wound; if infiltration of the whole volume is not possible, any remaining immunoglobulin should be given intramuscularly (in the anterolateral thigh and not the gluteal region) at a different site to that at which the vaccine was given.

Preparations

Ph. Eur.: Human Rabies Immunoglobulin;
USP 31: Rabies Immune Globulin.

Proprietary Preparations (details are given in Part 3)
Arg.: Imogam Rabia; ***Austral.:*** Imogam; ***Austria:*** Berirab; ***Canad.:*** BayRab†; Hyperrab; Imogam; ***Cz.:*** Favirab; Imogam Rabies†; ***Fr.:*** Imogam Rage; ***Ger.:*** Berirab; Tollwutglobulin; ***Hong Kong:*** BayRab; Rabumant†; ***India:*** Berirab-P; Carig; ***Indon.:*** Imogam; ***Israel:*** BayRab; Berirab; Imogam

Rabies; ***Mex.:*** BayRab†; Berirab-P; Kamrab; ***Philipp.:*** BayRab; Berirab-P; Favirab; ***S.Afr.:*** Rabigam; ***Singapore:*** BayRab†; ***Spain:*** Imogam Rabia; ***Switz.:*** Berirab; Rabuman; ***Thai.:*** Favirab; Imogam Rabies; Rabumun†; ***Turk.:*** Imogam; ***USA:*** HyperRab; Imogam Rabies; ***Venez.:*** Imogan Rabia†.

Rabies Vaccines

Vacunas de la rabia.

ATC — J07BG01.

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

Ph. Eur. 6.2 (Rabies Vaccine for Human Use Prepared in Cell Cultures; Vaccinum Rabiei ex Cellulis ad Usum Humanum; Rabies Vaccine BP 2008). A sterile freeze-dried suspension of inactivated rabies virus; a suitable strain is grown in an approved cell culture. The cell-culture medium may contain suitable antibacterials at the smallest effective concentration. The vaccine is prepared immediately before use by the addition of a suitable sterile liquid. The estimated potency is not less than 2.5 international units per dose. The dried vaccine should be stored at 2° to 8° and be protected from light.

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

USP 31 (Rabies Vaccine). A sterile preparation, in dried or liquid form, of inactivated rabies virus obtained from inoculated diploid cell cultures. It has a potency of not less than 2.5 international units per dose. It should be stored at 2° to 8°.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

Patients receiving human diploid-cell or purified chick embryo-cell rabies vaccines may experience pain, erythema, and induration at the injection site. Systemic reactions including abdominal pain, diarrhoea, nausea and vomiting, headache, chills, dizziness, fever, malaise, convulsions, encephalitis, lymphadenopathy, arthralgia and myalgia, dyspnoea and wheezing, or rash may also occur. Reactions may become more severe with repeated doses. Hypersensitivity reactions including anaphylaxis occur more commonly with vaccines prepared from non-human sources than with human diploid-cell vaccine. However, these reactions have also been associated with the presence of β-propiolactone-altered human albumin in the human diploid-cell vaccine.

Neurological reactions (meningoencephalitis, meningoencephalomyelitis, mononeuritis multiplex, transverse myelitis, or ascending paralysis) have been associated with the use of animal nerve-tissue vaccines. WHO considers that nerve-tissue vaccines should no longer be used. There are only isolated reports of neurological reactions after use of human diploid-cell vaccines.

Patients known to be hypersensitive to a particular vaccine or its components should be given an alternative product if available, although there are no absolute contra-indications to postexposure treatment. Pre-exposure prophylaxis should be delayed in patients with febrile illness until fever has resolved.

Effects on the nervous system. Rabies vaccines were originally prepared from infected animal brain tissue. The incidence of neurological complications with these vaccines was about 1 in 1 600, with an overall mortality of 15%.[1] Neurological adverse effects were attributed to myelin basic proteins present in these vaccines.[1-4] Subsequently, a highly immunogenic rabies vaccine was produced from the relatively myelin-free nerve tissue of suckling mice. However, neuroparalytic complications were reported in about 1 in 8 000 persons treated.[1,5] Most of these complications were of a Guillain-Barré-type illness, and had a fatality rate of 20 to 50%.[1]

Neuroparalytic reactions occur less frequently (1 in 32 000 persons treated) with vaccines prepared from duck embryo tissue;[1,5] however, these vaccines are no longer manufactured.[5]

Cell-derived rabies vaccines have been developed with better safety profiles.[1,5,6]

Isolated cases of neuroparalytic reactions have been reported with human diploid-cell or chick embryo-cell vaccines, mostly manifesting as a Guillain-Barré-type illness.[1,7-10]

1. Bernard KW, *et al.* Neuroparalytic illness and human diploid cell rabies vaccine. *JAMA* 1982; **248:** 3136–8.
2. WHO. WHO expert committee on rabies: eighth report. *WHO Tech Rep Ser 824* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_824.pdf (accessed 15/10/07)
3. Kulkarni V, *et al.* Biphasic demyelination of the nervous system following anti-rabies vaccination. *Neurol India* 2004; **52:** 106–8.
4. Siddiqui A, *et al.* Guillain-Barre syndrome occurring after rabies vaccination. *J Pakistan Med Assoc* 2005; **55:** 87–8.
5. Anonymous. Rabies vaccines. *Wkly Epidem Rec* 2002; **77:** 109–19.
6. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2004. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)
7. Knittel T, *et al.* Guillain-Barré syndrome and human diploid cell rabies vaccine. *Lancet* 1989; **i:** 1334–5.
8. Tornatore CS, Richert JR. CNS demyelination associated with diploid cell rabies vaccine. *Lancet* 1990; **335:** 1346–7.
9. Mortiere MD, Falcone AL. An acute neurologic syndrome temporally associated with postexposure treatment of rabies. *Pediatrics* 1997; **100:** 720–1.
10. Chakravarty A. Neurologic illness following post-exposure prophylaxis with purified chick embryo cell antirabies vaccine. *J Assoc Physicians India* 2001; **49:** 927–8.

Hypersensitivity. Systemic hypersensitivity reactions[1] have occurred in up to 6% of patients receiving booster immunisation with human diploid-cell rabies vaccine (HDCV), with onset after 2 to 21 days. Presenting features include generalised or pruritic rash or urticaria, angioedema, arthralgias, fever, nausea, and vomiting. These reactions have been linked to the presence of β-propiolactone-altered human albumin in HDCV. A lower risk of hypersensitivity reaction should exist with newer cell-derived vaccines that contain little or no human albumin, such as purified chick embryo cell rabies vaccines (PCECV) or purified Vero-cell rabies vaccines (PVRV). A review[2] noted that patients receiving booster immunisation with PCECV did not generally exhibit systemic hypersensitivity reactions. In a comparison study[3] involving 400 children, patients receiving a new chromatographically purified Vero-cell vaccine were found to have a lower incidence of systemic hypersensitivity (0.7%) than those in the HDCV group (1.2%) after booster immunisation.

1. Anonymous. Rabies vaccines. *Wkly Epidem Rec* 2002; **77:** 109–19.
2. Dreesen DW. A global review of rabies vaccines for human use. *Vaccine* 1997; **15** (suppl): S2–S6.
3. Sabchareon A, *et al.* A new Vero cell rabies vaccine: results of a comparative trial with human diploid cell rabies vaccine in children. *Clin Infect Dis* 1999; **29:** 141–9.

Spongiform encephalopathies. Possible transmission of Creutzfeldt-Jakob disease associated with sheep-brain rabies vaccine has been reported from India.[1] It was suggested that transmission of the abnormal prion protein from sheep with scrapie might be implicated.

1. Arya SC. Acquisition of spongiform encephalopathies in India through sheep-brain rabies vaccination. *Natl Med J India* 1992; **4:** 311–12.

Interactions

As for vaccines in general, p.2202.

Antimalarials. Studies have suggested that continuous antimalarial chemoprophylaxis with *chloroquine* during primary immunisation with human diploid-cell rabies vaccine, given intradermally for pre-exposure prophylaxis, may be associated with a poor antibody response.[1,2] WHO[3] recommends that people currently taking malaria prophylaxis or those unable to complete the 3-dose rabies pre-exposure regime before starting malaria prophylaxis should receive pre-exposure rabies vaccination by the intramuscular route instead.

1. Taylor DN, *et al.* Chloroquine prophylaxis associated with a poor antibody response to human diploid cell rabies vaccine. *Lancet* 1984; **i:** 1405.
2. Pappaioanou M, *et al.* Antibody response to preexposure human diploid-cell rabies vaccine given concurrently with chloroquine. *N Engl J Med* 1986; **314:** 280–4.
3. WHO. WHO expert consultation on rabies: first report. *WHO Tech Rep Ser 931* 2005. Also available at: http://libdoc.who.int/trs/WHO_TRS_931_eng.pdf (accessed 15/10/07)

Uses and Administration

Rabies vaccines are used for active immunisation against rabies. They are used as part of postexposure treatment to prevent rabies in patients who have been bitten by rabid animals or animals suspected of being rabid. Infection does not take place through unbroken skin but is possible through uninjured mucous membranes and has been reported after the inhalation of virus in the laboratory. Rabies vaccines are also used for pre-exposure prophylaxis against rabies in persons exposed to a high risk of being bitten by rabid or potentially rabid animals.

Schedules for prophylaxis and treatment of rabies are recommended by WHO (see Pre-exposure Immunisation, below) and many countries have immunisation schedules based on these.

In the UK, two types of rabies vaccine are available. The first type is prepared from inactivated Wistar rabies virus strain PM/WI38 1503-3M cultured on human diploid cells, and the second type is prepared from inactivated Flury LEP virus strain produced on purified chick embryo cells. Each contains not less than 2.5 international units/mL. The purified chick embryo-cell vaccine is given intramuscularly into the deltoid region in adults but into the anterolateral aspect of the thigh in children. The human diploid-cell vaccine is given intramuscularly into the deltoid region in both adults and children. Other cell culture-derived vaccines, such as Vero cell rabies vaccine, are available in other countries.

For **pre-exposure prophylaxis** against rabies, the recommended schedule in the UK is 3 doses, each of 1 mL, by intramuscular injection on days 0, 7, and 28; the third dose may in some instances be given on day 21 if there is insufficient time before travel. For persons at regular and continuous risk, a single reinforcing dose should be given 1 year after completion of the primary course with further doses at 3- to 5-year intervals. For those at intermittent risk, a booster dose should be given from 2 years after completion of the primary course.

For **postexposure treatment**, thorough cleansing of the wound with soap and water is imperative. The recommended schedule in the UK for unimmunised or incompletely immunised persons is 5 doses, each of 1 mL, by intramuscular injection on days 0, 3, 7, 14, and 30. In fully immunised persons two doses of vaccine should be given intramuscularly, one each on day 0 and day 3. Vaccination should be started as soon as possible after exposure, and may be stopped if it is proved that the patient was not at risk. In previously unimmunised patients at high risk, rabies immunoglobulin (see above) should also be given at the same time as the first dose of vaccine.

Rabies. Rabies is caused by infection with a rhabdovirus of the genus Lyssavirus. Rabies has a worldwide distribution, primarily in domesticated and wild dogs but also in bats and other warm-blooded animals, although some countries, including the UK, most of Australasia, and Antarctica are designated as rabies-free areas. Transmission of the rabies virus to humans is usually by the bite of an infected animal or contamination of broken skin by saliva. Infection is possible via intact mucous membranes and by aerosol transmission, but infection is unlikely after contamination of intact skin. Other body fluids such as urine and tears should be regarded as potentially infectious; rabies virus transmission has also been reported after organ transplantation from misdiagnosed donors.

Human rabies is almost always fatal once symptoms have appeared. The incubation period varies from 2 weeks to 6 years (average of 2 to 3 months) depending on the distance of the bite site from the brain and the amount of virus in the inoculum. There are 2 types of clinical presentations of rabies; encephalitic (furious) and paralytic (dumb). Encephalitic rabies presents with periods of hyperexcitability accompanied by severe agitation and bizarre behaviour alternating with periods of lucidity. Severe spasms of the larynx and pharynx may be provoked by attempts at swallowing (leading to hydrophobia) or by air blown at the face (aerophobia). Other symptoms include hypersalivation, fever, and convulsions. In the paralytic form, progressive flaccid paralysis develops in the bitten limb and ascends in a symmetrical or asymmetrical manner. Patients not dying through respiratory or cardiac arrest during the acute phase may develop any of a number of complications culminating in coma and death or (very rarely) recovery; only a few patients are documented as having survived after the onset of coma, and all had received either pre- or postexposure immunisation.

National control programmes involve epidemiological surveillance, mass canine immunisation campaigns, and dog population management. The development of oral animal vaccines delivered on baited food has met with considerable success in a number of areas and has become an essential tool for eliminating rabies in wild animals. Rigorously applied controls of international transfer of animals including certification of vaccination and quarantine for animals entering rabies-free areas are necessary to prevent re-introduction of rabies.

Although a number of treatments have been tried including antivirals, interferons, high doses of rabies immunoglobulin, and corticosteroids, none has shown evidence of effectiveness. Postexposure treatment after contact with a suspected or confirmed rabid animal may be effective in preventing death; it includes prompt and thorough cleansing of the contaminated site and the early use of rabies vaccine with or without rabies immunoglobulins. For a brief outline of postexposure treatment, see below.

Pre-exposure prophylaxis is recommended in persons at high risk of exposure, either due to their occupation or those travelling in enzootic areas. The main obstacle to mass pre-exposure vaccination appears to be the high cost of cell culture vaccines. See under Pre-exposure Immunisation (below) for outlines of recommended vaccination schedules.

Choice of vaccines. Many different rabies vaccines are available for human use. Some are derived from nerve tissue of animals, some from avian tissues (duck embryos), and some prepared in cell cultures. The first rabies vaccine was based on attenuated virus from desiccated nerve tissue. Later, inactivated nervous tissue-derived vaccines were prepared from rabid sheep, goat (Semple vaccines) or suckling mouse brains (Feunzalida Palacios vaccine). A complete postexposure treatment course of nerve-tissue vaccine consists of up to 23 injections and is associated with severe neurological reactions and a significant failure rate. WHO therefore strongly recommends that nerve-tissue vaccines should not be used, and that production should be stopped. Cell-derived rabies vaccines were subsequently developed; the human diploid cell rabies vaccine (HDCV) was introduced in 1967 and later less expensive purified chick embryo-cell vaccine (PCECV) and puri-