fied Vero-cell rabies vaccines (PVRV) entered use. There appears to be little difference in terms of safety and antigenicity between HDCV, PCECV, and PVRV in recommended regimens. The incidence of severe hypersensitivity reactions should, however, be lower with PVRV and PCECV than with HDCV since the purification process removes most human serum albumin in the cell-growth medium before virus inactivation (see Hypersensitivity, under Adverse Effects and Precautions, above). A purified duck-embryo vaccine (PDEV) provided similar efficacy and safety to vaccines produced from cell cultures, but is no longer manufactured.

There is little data concerning the efficacy of rabies vaccines. It appears that nerve-tissue vaccines afford limited protection after minor exposures to rabies virus, are less effective after head bites, and are of little use after very severe exposures. Failure rates for HDCV, PCECV, and PVRV (including cases with less than the recommended therapy) have been estimated as less than 1 in 80 000 treatments in the USA, Canada, and Europe, 1 in 12 000 to 20 000 in Thailand, and 1 in 30 000 in the remaining tropical countries. Reported failures of these vaccines are usually associated with severe lesions on or near the head and/or errors in treatment, such as deviation from recommendations, incorrect site of vaccine administration, or delay in treatment. WHO recommends a minimum potency of 2.5 international units per intramuscular dose for all cell-derived rabies vaccines.

The cost of cell-derived rabies vaccines is prohibitively high in the developing world. Although the adverse effects of nerve-tissue vaccines preclude their use for pre-exposure prophylaxis, they are still used in some countries for postexposure prophylaxis. WHO is anxious that nerve-tissue vaccines should be replaced with affordable cell-derived vaccines as soon as possible. In the meantime, cost-cutting regimens have been devised for use of cell-derived rabies vaccines by the intradermal route. Rapid immunisation is achieved by the use of several sites of injection; fewer injections are required than with traditional intramuscular regimens.

PRE-EXPOSURE IMMUNISATION. WHO[1,2] has developed guidelines as to who should receive pre-exposure vaccination with rabies vaccines. However, national policies may vary somewhat from that of WHO, depending on the local risk of contracting rabies and the vaccines available; it is generally recommended for use in persons at high risk of infection with rabies virus. Where available, the vaccines produced in cell culture or from purified embryonated eggs are preferred over the vaccines produced in animal tissues (see under Choice of Vaccine, above). WHO recommends[1,2] pre-exposure prophylaxis for persons regularly at high risk of exposure, such as certain laboratory workers, veterinarians, animal handlers, and wildlife officers, and those living in or travelling to areas where rabies is endemic (particularly in children under 15 years of age). The immunisation schedule should preferably consist of 3 injections of a rabies vaccine of potency at least 2.5 international units given on days 0, 7, and either day 21 or 28, but variation of a few days is unimportant. Vaccine should be given into the deltoid area of the arm or for young children into the anterolateral area of the thigh. Titres of virus-neutralising antibodies can be checked in serum samples collected 1 to 3 weeks after the last dose. Those who work with the live virus should have their antibody titres checked every 6 months and if the figure falls below 0.5 international units/mL they should receive a booster.[1,2] Other individuals at continuing risk should have their titres checked every 12 months and a booster given if the titre is below 0.5 international units/mL.[1]

WHO also suggests intradermal use of rabies vaccine in doses of 0.1 mL on days 0, 7, and either day 21 or 28 but intramuscular injection is preferable and is mandatory in those taking malaria prophylaxis.

In the UK,[3] the schedule for immunisation (see Uses and Administration, above) is similar to that recommended by WHO.

In the USA, immunisation with a human diploid cell vaccine, a vaccine adsorbed onto an aluminium salt, or a purified chick embryo cell vaccine is carried out similarly to the WHO schedule, with serum-antibody titres determined every 6 months to 2 years, depending upon the level of exposure, and booster doses given as necessary.[4]

1. 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)
2. 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)
3. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 15/07/08)
4. CDC. Human rabies prevention—United States, 1999: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1999; **48** (RR-1): 1–21. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr4801.pdf (accessed 25/05/06)

POSTEXPOSURE TREATMENT. WHO guidelines[1,2] emphasise the importance of prompt local treatment for all bite wounds and scratches that may be contaminated with rabies virus and that, depending on the category of animal contact, rabies vaccine on its own or with rabies immunoglobulin should be given. The combination of these measures immediately after exposure is considered to guarantee almost complete protection. Pregnancy and infancy are not contra-indications to postexposure vaccination. These measures should be instituted even in patients who present months after having been bitten.

First aid or local treatment consists of immediate thorough flushing and washing of the wound with water, or soap and water, or detergent followed by the application of alcohol 70% or tincture or aqueous solution of iodine. Medical care may then consist of the instillation of rabies immunoglobulin into the depth of the wound and infiltration around the wound. Ideally the wound should not be sutured, but if suturing is necessary then it is essential that it be preceded by rabies immunoglobulin as above. Antimicrobials and tetanus vaccine may also be given as necessary.

The use of rabies vaccine and of rabies immunoglobulin depends on the category of animal contact. WHO classifies the type of contact with a suspect or rabid animal into 3 categories:

- category I covers touching or feeding of animals and licks on intact skin
- category II covers nibbling of uncovered skin, minor scratches or abrasions without bleeding, and licks on broken skin
- category III covers single or multiple transdermal bites or scratches and contamination of mucous membranes with the animal's saliva

Generally no treatment is required for category I contact. Patients who have had category II contact should be given rabies vaccine but the course may be stopped if the contact has been with a cat or dog that remains healthy throughout an observation period of 10 days or if postmortem study of the contact animal shows it to be negative for rabies. Patients with category III contact should be given rabies vaccine preceded by rabies immunoglobulin infiltrated around the wound and instilled into it as described above.

There are 2 types of immunoglobulin available; human rabies immunoglobulin (HRIG) and pepsin-digested or highly purified equine rabies immunoglobulin (ERIG). The recommended dose for HRIG is 20 international units/kg and for ERIG products is 40 international units/kg. As much as possible of the dose should be infiltrated into and around the wound, with the remainder being injected intramuscularly into a site remote from that where vaccine was given, such as the anterior thigh.

The potency of rabies vaccines should be at least 2.5 international units per single human dose. For intramuscular vaccination schedules one dose should be given on days 0, 3, 7, 14, and 28 into the deltoid region or, for small children, into the anterolateral area of the thigh. An abbreviated multisite intramuscular schedule (the 2-1-1 regimen) induces an early antibody response and may be particularly effective when postexposure treatment has not included a rabies immunoglobulin. This schedule consists of one dose given in the right arm and one in the left arm on day 0, and one dose intramuscularly into the deltoid region on days 7 and 21.

Intradermal vaccination reduces the volume of injection required and is therefore suited to situations where vaccine or money is in short supply. For intradermal vaccination one dose (0.1 mL) of purified chick embryo-cell or purified Vero-cell vaccine may be given at each of two sites, usually the left and right upper arm, on days 0, 3, 7, and 28. Alternatively, in emergency situations when no rabies immunoglobulin is available, either human diploid cell or purified chick embryo-cell rabies vaccine may be given intradermally in one dose at each of 8 sites on day 0, in one dose at 4 sites on day 7, and subsequently in one dose at one site on days 28 and 90.

For postexposure treatment of previously vaccinated patients, WHO recommends local treatment of wounds followed by rabies vaccine given on days 0 and 3, either as a standard intramuscular dose or as one intradermal dose per site. No rabies immunoglobulin should be given. Patients who previously received vaccines of unproven potency or who have failed to develop an acceptable rabies neutralising antibody titre should be given full treatment as for those previously unimmunised.

In the UK,[3] rabies immunoglobulin is given if the patient is previously unimmunised and at high risk. Vaccine is given on days 0, 3, 7, 14, and 30 (five doses) in unimmunised persons (although the UK licensed product information for human diploid cell vaccine also recommends a sixth dose on day 90); two doses, one each on day 0 and day 3 are given to previously fully immunised persons.

In the USA, a human diploid-cell vaccine, an adsorbed rabies vaccine, or a purified chick embryo cell vaccine may be used for postexposure treatment.[4] In previously unimmunised individuals, a 1-mL dose of vaccine is given intramuscularly on days 0, 3, 7, 14, and 28, with rabies immunoglobulin as in the WHO schedule. In previously immunised individuals, two doses of vaccine are given on days 0 and 3, and rabies immunoglobulin is not required.

1. 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)
2. 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)
3. Department of Health. *Immunisation Against Infectious Disease* 2006: "The Green Book". Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917?IdcService=GET_FILE&dID=115974&Rendition=Web (accessed 15/07/08)
4. CDC. Human rabies prevention—United States, 1999: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1999; **48** (RR-1): 1–21. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr4801.pdf (accessed 25/05/06)

Preparations

Ph. Eur.: Rabies Vaccine for Human Use Prepared in Cell Cultures; ***USP 31:*** Rabies Vaccine.

Proprietary Preparations (details are given in Part 3)
Arg.: Verorab; ***Austral.:*** Rabipur; ***Austria:*** Rabipur; ***Braz.:*** HDCV; Vacina Anti-Rabica Humana; Verorab†; ***Canad.:*** Imovax Rabies; RabAvert; ***Chile:*** Verorab; ***Cz.:*** Rabipur; Verorab; ***Denm.:*** Rabies-Imovax; ***Fin.:*** Rabies-Imovax; ***Fr.:*** Rabipur; ***Ger.:*** Rabipur; Rabivac†; Tollwut-Impfstoff (HDC); ***Hong Kong:*** Verorab; ***India:*** Rabipur; Rabivax; ***Indon.:*** Verorab; ***Israel:*** Rabipur; ***Ital.:*** Imovax Rabbia; Lyssavac N†; Rabipur; Rasilvax†; ***Malaysia:*** Verorab; ***Neth.:*** Rabipur; ***Norw.:*** Rabies-Imovax; ***Philipp.:*** Rabipur; Verorab; ***Pol.:*** Verorab; ***Port.:*** Rabipur; ***S.Afr.:*** Rabipor; Verorab; ***Spain:*** Vacuna Antirrabica; ***Swed.:*** Rabies-Imovax; ***Switz.:*** Lyssavac N†; ***Thai.:*** Lyssavac N; Rabipur; Verorab; ***Turk.:*** HDCV; Rabivac; ***UK:*** Rabipur; ***USA:*** Imovax Rabies; RabAvert; ***Venez.:*** Verorab.

Respiratory Syncytial Virus Immunoglobulins

Inmunoglobulinas contra el virus sincitial respiratorio.

Palivizumab *(BAN, rINN)*

Palivitsumabi; Palivizumabum. immunoglobulin G 1 (human-mouse monoclonal MEDI-493 γ1-chain antirespiratory syncytial virus protein F), disulfide with human-mouse monoclonal MEDI-493 κ-chain, dimer.

Паливизумаб
CAS — 188039-54-5.
ATC — J06BB16.

Adverse Effects and Precautions
As for immunoglobulins in general, p.2201.

Interactions
As for immunoglobulins in general, p.2201.

There is some evidence that antibody responses to diphtheria, tetanus, pertussis, and Haemophilus influenzae vaccines may be reduced in infants also receiving respiratory syncytial virus immunoglobulins.

Uses and Administration
Respiratory syncytial virus immunoglobulin is available in some countries for the passive immunisation of infants against lower respiratory-tract infections caused by RSV. It is prepared from the pooled plasma of adults selected for high titres of antibodies that neutralise the virus. Each mL of respiratory syncytial virus immunoglobulin contains about 50 mg of protein.

In the USA, children under 2 years of age with chronic lung disease (bronchopulmonary dysplasia) or a history of premature birth may receive a prophylactic intravenous infusion once a month during the RSV season (typically November to April or early May). The drug is given in a dose of up to 750 mg/kg at an initial rate of 75 mg/kg per hour for 15 minutes, followed by 180 mg/kg per hour until the end of the infusion.

Palivizumab, a human monoclonal antibody to RSV, is available in some countries and is used intramuscularly for similar purposes, in a dose of 15 mg/kg monthly. Palivizumab is also recommended in children under 2 years of age with haemodynamically significant congenital heart disease. Children undergoing cardiac bypass should be given an extra dose of palivizumab as soon as they are stable after surgery; doses are subsequently resumed monthly thereafter.

◊ The American Academy of Pediatrics has issued revised indications for the use of palivizumab and respiratory syncytial virus immunoglobulin.[1] Palivizumab or respiratory syncytial virus immunoglobulin prophylaxis should be considered for infants younger than 2 years of age with chronic lung disease (bronchopulmonary dysplasia) who have required medical therapy for their condition within 6 months of the anticipated start of the RSV season. Infants born at 32 weeks' gestation or earlier may benefit from prophylaxis even if they do not have chronic lung disease. Although prophylaxis has been shown to reduce hospitalisation for infants born between 32 and 35 weeks' gestation, the cost for this large group of infants should be considered carefully. Palivizumab, may in addition be given to children under 2 years of age with haemodynamically significant congenital heart disease.

Both palivizumab and respiratory syncytial virus immunoglobulin have been shown to decrease the risk of severe RSV infection in high-risk infants and children. Palivizumab is preferred over respiratory syncytial virus immunoglobulin for most high-risk children because of its comparative ease of administration, safety, and efficacy. Monthly use of palivizumab during the RSV season results in a 45 to 55% reduction in hospitalisation. Although palivizumab is usually preferred, respiratory syncytial virus immunoglobulin may also decrease the incidence of other respiratory-tract infections in addition to those caused by RSV, and this may be of benefit for infants younger than 6 months who are not eligible for influenza immunisation and those with severe pulmonary disease who may be more prone to other respiratory-tract infections. Palivizumab has not been shown to affect the rate of hospitalisation for non-RSV infections or the incidence of otitis media.

1. Committee on Infectious Diseases and Committee on Fetus and Newborn, American Academy of Pediatrics. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics* 2003; **112:** 1442–6. Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;112/6/1442.pdf (accessed 24/05/06)