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)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Synagis; ***Austral.:*** Synagis; ***Belg.:*** Synagis; ***Braz.:*** Synagis; ***Canad.:*** Synagis; ***Chile:*** Synagis; ***Cz.:*** Synagis; ***Denm.:*** Synagis; ***Fin.:*** Synagis; ***Fr.:*** Synagis; ***Ger.:*** Synagis; ***Gr.:*** Synagis; ***Hong Kong:*** Synagis; ***Hung.:*** Synagis; ***Irl.:*** Synagis; ***Israel:*** Abbosynagis; ***Ital.:*** Synagis; ***Malaysia:*** Synagis; ***Mex.:*** Synagis; ***Neth.:*** Synagis; ***Norw.:*** Synagis; ***NZ:*** Synagis; ***Pol.:*** Synagis; ***Port.:*** Synagis; ***S.Afr.:*** Synagis; ***Singapore:*** Synagis†; ***Spain:*** Synagis; ***Swed.:*** Synagis; ***Switz.:*** Synagis; ***Turk.:*** Synagis; ***UK:*** Synagis; ***USA:*** RespiGam; Synagis; ***Venez.:*** Synagis.

Respiratory Syncytial Virus Vaccines

Vacunas del virus sincitial respiratorio.

Profile

Vaccines containing RSV protein subunit are being studied for active immunisation.

◊ Development of an effective and safe vaccine against RSV has been hampered by a number of factors.[1-3] The target population for a vaccine is mainly young infants who may not respond adequately to vaccination owing to the antigenic diversity of RSV, immunological immaturity, or the presence of maternal antibodies. In the early 1960s, a formalin inactivated respiratory syncytial virus vaccine known as FI-RSV (also sometimes called Lot 100) was tested in infants and children aged 2 months to 7 years but failed to protect against subsequent infection with wild-type virus; it also led to a catastrophically exaggerated clinical response to wild-type virus in infants who were naive to RSV before vaccination, resulting in hospitalisation for the majority of recipients and 2 fatalities. Since that time, a number of candidate vaccines have subsequently been developed including live attenuated virus and viral protein subunit vaccines.[1,2] Several of the live attenuated vaccine candidates have been investigated in humans but results have generally been disappointing. More recently, genetically engineered live attenuated vaccine candidates have been generated, and some are currently being investigated in clinical studies.[1,2]

Subunit vaccines are composed of the F and G glycoproteins from RSV since these are the glycoproteins that induce antibody responses.[1,2] They are most likely to be of use in older persons and in high-risk children and might also be used for maternal immunisation. A chimeric FG fusion protein vaccine was evaluated in phase I studies but is no longer in development.

1. Durbin AP, Karron RA. Progress in the development of respiratory syncytial virus and parainfluenza virus vaccines. *Clin Infect Dis* 2003; **37:** 1668–77.
2. Kneyber MCJ, Kimpen JLL. Advances in respiratory syncytial virus vaccine development. *Curr Opin Investig Drugs* 2004; **5:** 163–70.
3. Power UF. Respiratory syncytial virus (RSV) vaccines—two steps back for one leap forward. *J Clin Virol* 2008; **41:** 38–44.

Rift Valley Fever Vaccines

Vacunas de la fiebre del valle del Rift.

Profile

An inactivated rift valley fever vaccine has been developed for the active immunisation of persons at high risk of contracting the disease.

Rotavirus Vaccines

Vacunas de rotavirus.

ATC — J07BH01; J07BH02.

Adverse Effects and Precautions

As for vaccines in general, p.2201.

The most common adverse effects reported in subjects receiving rotavirus vaccines (attenuated human strain or pentavalent reassortant rotavirus vaccine) are fever, fatigue, irritability, and gastrointestinal disturbances. Otitis media, nasopharyngitis, bronchospasm, and haematochezia (blood in the stools) have also been reported with the pentavalent vaccine. A few cases of Kawasaki disease have been reported with the pentavalent vaccine but no causal relationship has been established.

There has been much debate on the causal role of rotavirus vaccines for intussusception (see below); cases have been reported during post-marketing use.

The UK licensed product information for the attenuated human strain vaccine contraindicates the use of this vaccine in children with a history of intussusception or with congenital conditions of the gastrointestinal tract, while the US licensed product information for pentavalent vaccine advises that it be used with caution. Caution is also generally advised in those with gastrointestinal illnesses or growth retardation and use may be postponed in children suffering from diarrhoea or vomiting. Use of a rotavirus vaccine should be carefully considered before being given to infants with a close family contact who is immunocompromised; if given precautions should be taken to avoid transmission of any excreted vaccine virus.

Intussusception. A live oral tetravalent vaccine (RRV-TV) became available in the USA in August 1998 but was withdrawn from the market by the manufacturer in October 1999 after reports of intussusception (a condition when part of the intestine prolapses into the lumen of an adjacent part causing an obstruction). From September 1998 until July 1999, 15 patients with intussusception had been reported to the Vaccine Adverse Event Reporting System (VAERS), 12 of whom developed symptoms within a week of vaccination.[1] While this evidence was considered inconclusive, further studies were expected to clarify the risks associated with routine use of this vaccine. One such study,[2] in which 429 infants with intussusception were retrospectively analysed, found that 74 (17.2%) had received RRV-TV compared with 226 of 1763 controls (12.8%) and concluded that there was evidence of a causal relationship with the vaccine. Another retrospective study,[3] however, found that there was no evidence of an increase in hospital admissions due to intussusception during the period of RRV-TV availability and recommended that a large, randomised, double-blind vaccine trial be performed to determine the absolute risk. Further analysis of the incidence of intussusception associated with RRV-TV has prompted discussion as to whether the absolute risk might in fact be sufficiently low that withholding the vaccine results in greater mortality than would be caused by intussusception.[4] Reassessment of the data on RRV-TV and intussusception has suggested that the risk for intussusception was age-dependent; relative risk for intussusception following the first dose of RRV-TV increased with increasing age.[5,6] However, WHO Global Advisory Committee on Vaccine Safety found that there was insufficient evidence available to determine whether use of RRV-TV before 60 days of age was associated with a lower risk for intussusception but confirmed the association of a high risk of intussusception in infants immunised after day 60.[7] Such considerations have implications for the ongoing evaluation of other candidate live attenuated rotavirus vaccines in that, should cases of intussusception occur, a decision might be required as to what constitutes an acceptable rate.[4]

From February 2006 until February 2007, 35 patients with confirmed intussusception had been reported to VAERS following vaccination with the pentavalent reassortant vaccine; 17 of whom developed symptoms within 21 days of vaccination, including 11 that occurred within 7 days of vaccination. However, this number of cases is not higher than the age adjusted background rates for intussusception.[8]

1. CDC. Intussusception among recipients of rotavirus vaccine—United States, 1998-1999. *MMWR* 1999; **48:** 577–81.
2. Murphy TV, *et al.* Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med* 2001; **344:** 564–72. Correction. *ibid.*; 1564.
3. Simonsen L, *et al.* Effect of rotavirus vaccination programme on trends in admission of infants to hospital for intussusception. *Lancet* 2001; **358:** 1224–9.
4. Murphy BR, *et al.* Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions. *J Infect Dis* 2003; **187:** 1301–8.
5. Rothman KJ, *et al.* Age dependence of the relation between reassortant rotavirus vaccine (RotaShield) and intussusception. *J Infect Dis* 2006; **193:** 898.
6. Simonsen L, *et al.* More on RotaShield and intussusception: the role of age at the time of vaccination. *J Infect Dis* 2005; **192** (suppl 1): S36–S43.
7. WHO. Global Advisory Committee on Vaccine Safety, 1–2 December 2005. *Wkly Epidem Rec* 2006; **81:** 15–19.
8. CDC. Postmarketing monitoring of intussusception after RotaTeq vaccination—United States, February 1, 2006–February 15, 2007. *MMWR* 2007; **56:** 218–22.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Several live oral rotavirus vaccines for use in the prevention of childhood diarrhoea have been developed and some are now licensed.

A live attenuated oral monovalent rotavirus vaccine (based on the human RIX4414 strain) is available in some countries. Two doses are given, the first at 6 weeks of age onwards and the subsequent dose at least 4 weeks later; the course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks. A live oral pentavalent reassortant rotavirus vaccine (based on human and bovine strains) is available in the USA. Three doses are given, the first at 6 to 12 weeks of age and the two subsequent doses at 4- to 10-week intervals; the third dose should not be given after 32 weeks of age.

A live oral tetravalent rotavirus vaccine (RRV-TV) was formerly available in the USA but was withdrawn by the manufacturer in October 1999 after reports of intussusception associated with its use.

◊ References.

1. Vesikari T, *et al.* Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006; **354:** 23–33.
2. Ruiz-Palacios GM, *et al.* Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; **354:** 11–22.
3. Buttery JP, Kirkwood C. Rotavirus vaccines in developed countries. *Curr Opin Infect Dis* 2007; **20:** 253–8.
4. Cunliffe N, Nakagomi O. Introduction of rotavirus vaccines in developing countries: remaining challenges. *Ann Trop Paediatr* 2007; **27:** 157–67.
5. Dennehy PH. Rotavirus vaccines: an overview. *Clin Microbiol Rev* 2008; **21:** 198–208.

Vaccine development. Rotaviruses are an important cause of severe diarrhoea in both developed and developing countries (see Gastro-enteritis, p.850); rates of illness are similar in both and improvement in water quality and general hygiene does not have much effect on viral transmission. The disease infects almost all children before the age of 5 years but is most severe among children 3 to 35 months of age.[1,2] Human rotavirus diarrhoea is caused by group A, B, or C rotaviruses.[3] While an initial infection does not produce complete immunity, it does appear to be protective against further severe gastroenteritis. Vaccination therefore aims to produce a similar effect.[1,2] Development of a suitable vaccine has been made difficult by the diversity of rotaviruses.[3] Initial attempts at vaccine development used single bovine or rhesus monkey strains but these were associated with variable efficacy and adverse effects.[4-6]

To overcome these problems reassortant rotavirus (RRV) strains were constructed. These combined animal rotavirus strains with human rotavirus genes coding for serotype-specific antigens, enabling polyvalent vaccines to be produced against the major rotavirus serotypes causing disease. A number of such candidate vaccines are under development[7] and some are now licensed.[8] Guidelines have been developed in the USA for the use of rotavirus vaccine.[1,2]

1. CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006; **55** (RR-12): 1–13. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5512.pdf (accessed 19/06/07)
2. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of rotavirus disease: guidelines for use of rotavirus vaccine. *Pediatrics* 2007; **119:** 171–82. Also available at: http://pediatrics.aappublications.org/cgi/reprint/119/1/171 (accessed 19/06/07)
3. Anonymous. Puzzling diversity of rotaviruses. *Lancet* 1990; **335:** 573–5.
4. Levine MM. Modern vaccines: enteric infections. *Lancet* 1990; **335:** 958–61.
5. Bernstein DI, *et al.* Evaluation of WC3 rotavirus vaccine and correlates of protection in healthy infants. *J Infect Dis* 1990; **162:** 1055–62.
6. Flores J, *et al.* Protection against severe rotavirus diarrhoea by rhesus rotavirus vaccine in Venezuelan infants. *Lancet* 1987; **i:** 882–4.
7. Glass RI, *et al.* The future of rotavirus vaccines: a major setback leads to new opportunities. *Lancet* 2004; **363:** 1547–50.
8. Heaton PM, Ciarlet M. Vaccines: the pentavalent rotavirus vaccine: discovery to licensure and beyond. *Clin Infect Dis* 2007; **45:** 1618–24.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Rotarix; RotaTeq; ***Austral.:*** Rotarix; RotaTeq; ***Belg.:*** Rotarix; ***Chile:*** Rotarix; ***Cz.:*** Rotarix; RotaTeq; ***Fr.:*** Rotarix; RotaTeq; ***Gr.:*** Rotarix; RotaTeq; ***Hung.:*** Rotarix; RotaTeq; ***Malaysia:*** Rotarix; RotaTeq; ***Mex.:*** Rotarix; ***NZ:*** Rotarix; RotaTeq; ***Philipp.:*** Rotarix; ***Pol.:*** Rotarix; RotaTeq; ***Port.:*** Rotarix; RotaTeq; ***Singapore:*** Rotarix; ***Thai.:*** Rotarix; ***UK:*** Rotarix; ***USA:*** Rotarix; RotaTeq; ***Venez.:*** Rotarix.

Rubella Immunoglobulins

Inmunoglobulinas contra la rubéola.

ATC — J06BB06.

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

Ph. Eur. 6.2 (Human Rubella Immunoglobulin; Immunoglobulinum Humanum Rubellae). A liquid or freeze-dried preparation containing immunoglobulins, mainly immunoglobulin G (IgG). It is obtained from plasma containing specific antibodies against the rubella virus. Normal immunoglobulin may be added. It contains not less than 4500 international units/mL. Both the liquid and freeze-dried preparations should be stored, protected from light, in a colourless, glass container. The freeze-dried preparation should be stored under vacuum or under an inert gas.

Adverse Effects and Precautions

As for immunoglobulins in general, p.2201.

Interactions

As for immunoglobulins in general, p.2201.

Uses and Administration

Rubella immunoglobulins may be used for passive immunisation against rubella (German measles). They have been used to prevent or modify rubella in susceptible persons.

Preparations

Ph. Eur.: Human Rubella Immunoglobulin.

Rubella Vaccines

Vacunas de la rubéola.

ATC — J07BJ01.

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

Ph. Eur. 6.2 (Rubella Vaccine (Live); Vaccinum Rubellae Vivum). A freeze-dried preparation of a suitable live attenuated strain of rubella virus grown in human diploid cell cultures. It is reconstituted immediately before use. The cell-culture medium may contain a permitted antibacterial at the smallest effective concentration, and a suitable stabiliser may be added to the bulk vaccine. The final vaccine contains not less than 3.0 log $CCID_{50}$ per dose. The dried vaccine should be stored at 2° to 8° and be protected from light.

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

USP 31 (Rubella Virus Vaccine Live). A bacterially sterile preparation of a suitable live strain of rubella virus grown in cultures of duck-embryo tissue or human tissue. It contains the equivalent of not less than 1×10^3 $TCID_{50}$ in each immunising dose. It should be stored at 2° to 8° and be protected from light.

Adverse Effects

As for vaccines in general, p.2201.

Generally, adverse effects have not been severe. Those occurring most commonly are skin rashes, pharyngitis,