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,