

3.18 ROTAVIRUS

Virology

Rotaviruses are non-enveloped RNA viruses in the family Reoviridae. Rotaviruses are classified according to the 2 surface proteins they contain: VP7, the glycoprotein (G protein), and VP4, the protease-cleaved protein (P protein). The G and P proteins are targets for neutralising antibodies thought to be necessary for protection.^{1,2} Because the 2 gene segments that encode these proteins can segregate independently, a typing system consisting of both P and G types has been developed. Rotavirus strains are most commonly referred to by their G serotype, with G1, G2, G3, G4 and G9 accounting for around 90% of serotypes both globally and in Australia.^{3,4} The most common P types found in combination with these G types are P1a[8] (found with all common G-types except G2) or P1b[4], usually found in combination with G2.⁵

Rotaviruses are shed in high concentrations in the stools of infected children and are transmitted by the faecal-oral route, both through close person-to-person contact and via fomites.⁶ Rotaviruses are probably also transmitted by other modes, such as faecally contaminated food, water and respiratory droplets.^{7,8}

Clinical features

Rotavirus is the predominant agent of severe dehydrating gastroenteritis in infants and young children in both developed and developing countries.^{1,2} The spectrum of rotavirus illness ranges from asymptomatic infection, to mild, watery diarrhoea of limited duration, to severe dehydrating diarrhoea with vomiting, fever, electrolyte imbalance, shock and death. Rotavirus infections are often more severe than other common causes of diarrhoea, and are more likely to be associated with dehydration and hospitalisation.^{1,7} The incubation period is 1 to 3 days, after which illness can begin abruptly with vomiting often preceding the onset of diarrhoea.⁷ Up to one-third of patients have a temperature of $>39^{\circ}\text{C}$ in the first few days of illness. Symptoms generally resolve in 3 to 7 days.

Epidemiology

Although individuals can be infected with rotavirus several times during their lives, the first infection, typically between 3 and 36 months of age, is most likely to cause severe diarrhoea and dehydration.^{9,10} After a single natural infection, 40% of children are protected against any subsequent infection with rotavirus, 75% are protected against diarrhoea from a subsequent rotavirus infection, and 88% are protected against severe diarrhoea.¹⁰ Repeat infections provide even greater protection. Disease is also less likely when reinfection occurs with a serotype (G type) to which an individual has already been exposed.

In Australia, the best available estimates are that approximately 10 000 hospitalisations due to rotavirus in children <5 years of age occur each year.¹¹ As such, rotavirus accounts for around half the hospitalisations for acute gastroenteritis of any cause in this age group.^{11,12} This translates to 3.8% of children (1 in 27) being hospitalised with rotavirus gastroenteritis by the age of 5 years. In addition to hospitalised children, an estimated 115 000 children <5 years of age visit a GP, and 22 000 children require an Emergency Department visit.^{11,13} On average, there is 1 death attributed to rotavirus each year in Australia, but this is likely to be a minimum estimate.¹³

In temperate Australia, rotavirus infections follow a seasonal pattern, the peak incidence being in mid to late winter. In the northern tropical and arid regions, there is no consistent seasonal pattern and disease peaks are unpredictable.¹⁴ Epidemics of rotavirus gastroenteritis have occurred in Central Australia, causing severe strain on healthcare services.^{15,16} Overall, Indigenous Australian infants and children are hospitalised with rotavirus gastroenteritis about 3 to 5 times more commonly than their non-Indigenous peers, have a younger age at hospitalisation, and longer duration of hospital stay (an average of 5 days compared with 2 days for non-Indigenous infants).^{12,14,15,17}

Children and adults with impaired immunity, such as those with congenital immunodeficiency, or post haematopoietic or solid organ transplantation, are at increased risk of severe, prolonged, and even fatal rotavirus gastroenteritis.^{1,18,19} Rotavirus is an important cause of nosocomial gastroenteritis,²⁰⁻²⁴ and can also cause disease in adults, especially those caring for children, and outbreaks of gastroenteritis in aged care facilities.^{1,25,26}

Vaccines

Two oral rotavirus vaccines are available in Australia, and data on their immunogenicity, safety and efficacy has been systematically reviewed.²⁷ Both vaccines are live attenuated vaccines administered orally to infants, but the component vaccine viruses differ. Rotarix (GlaxoSmithKline) is a live attenuated vaccine containing 1 strain of attenuated human rotavirus (G1P1[8] strain). The human live attenuated strain protects against non G1 serotypes on the basis of their common P[8] antigen and other epitopes involved in heterotypic immunity. RotaTeq (CSL Biotherapies/Merck & Co Inc) is a pentavalent vaccine containing 5 human-bovine rotavirus reassortants with the human serotypes G1, G2, G3, G4, and P1[8] and the bovine serotypes G6 and P7. The vaccine viruses replicate in the intestinal mucosa and can be shed in the stool of vaccine recipients, particularly after the first dose. Vaccine virus shedding is more common with Rotarix and is detected in the stool a week after vaccination in up to 80% of first dose recipients, and in up to 30% of second dose recipients.²⁷⁻²⁹ RotaTeq is only shed after the first dose (in up to 13% of recipients).³⁰ There have been no studies to assess the implications of shedding for horizontal spread to contacts.

Current oral rotavirus vaccines are underpinned by decades of developmental work.³¹ Randomised placebo-controlled studies of both vaccines have documented their efficacy and safety in the prevention of gastroenteritis caused by rotavirus.^{27,30,32} A vaccination course prevents rotavirus gastroenteritis of any severity in approximately 70% of recipients over the following 1 to 2 years. The efficacy against severe rotavirus gastroenteritis and against hospitalisation for rotavirus gastroenteritis is higher, ranging from 85 to 100% in clinical trials in many different countries.^{27,30,32,33} Efficacy in the prevention of hospitalisation from rotavirus gastroenteritis ranged from 85 to 100%.^{27,30,32,33} Vaccination was also highly effective in preventing Emergency Department and clinic/GP visits.^{30,33} Overall, rotavirus vaccination prevented around half (42–58%) of hospital admissions for acute gastroenteritis of any cause in young children, suggesting that rotavirus is responsible for more gastroenteritis than detected using routine testing and admission practices.^{30,32,33} In randomised control trials, a degree of protection against rotavirus gastroenteritis was also observed in infants who received fewer than the recommended number of doses of rotavirus vaccines. In the available clinical trials, no statistically significant differences were found between the 2 vaccines with regard to protective efficacy by serotype.^{27,30,32} The efficacy and safety of both rotavirus vaccines have been evaluated only in clinical trials in which infants received vaccine within specified age limits. There are no data on the use of rotavirus vaccines outside these age ranges (see ‘Recommendations’ and ‘Adverse events’ below).

- **Rotarix** – GlaxoSmithKline (live attenuated RIX4414 human rotavirus strain expressing G1P1[8] outer capsid proteins). Each 1.0 mL monodose of the reconstituted vaccine contains not less than $10^{6.0}$ CCID₅₀ (cell culture infectious dose 50%) of the RIX4414 strain; sucrose; dextran 40; sorbitol; amino acids; Dulbecco’s Modified Eagle Medium; calcium carbonate; xanthan gum. Calcium carbonate buffer solvent (diluent) supplied for reconstitution.
- **RotaTeq** – CSL Biotherapies/Merck & Co Inc (live, oral pentavalent vaccine). Each 2.0 mL monodose pre-filled dosing tube contains rotavirus reassortants G1, G2, G3, G4 and P1[8] each with a minimum dose level of at least 2.0×10^6 infectious units; sucrose; sodium citrate; sodium phosphate monobasic monohydrate; sodium hydroxide; polysorbate 80; cell culture media; trace amounts of fetal bovine serum. Also available in packs of 10 monodose pre-filled dosing tubes.

Transport, storage and handling

Transport both vaccines according to *National Vaccine Storage Guidelines: Strive for 5*.³⁴ Store at +2°C to +8°C. Do not freeze. Protect from light.

Dosage and administration

Rotavirus vaccines are for oral administration only. Under *no* circumstances should rotavirus vaccines be injected.

There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination with either rotavirus vaccine.^{7,35}

Rotarix is recommended for use in a 2-dose course (at 2 and 4 months of age). It is presented as a white powder for reconstitution with a separately supplied diluent, and a transfer adapter. The syringe/oral plunger containing the diluent is attached to the vial of lyophilised powder via the transfer adapter, and following reconstitution the 1 mL dose of vaccine should be administered *orally* via the syringe/oral plunger onto the inside of the infant's cheek.

RotaTeq is recommended for use in a 3-dose course (at 2, 4, and 6 months of age). It is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct *oral* administration of the 2 mL dose onto the inside of the infant's cheek. RotaTeq does not require reconstitution or dilution. RotaTeq is a pale yellow, clear liquid that may have a pink tint.

Rotavirus vaccines can be co-administered with other vaccines included on the NIP schedule at 2 and 4 months of age (Rotarix) or 2, 4 and 6 months of age (RotaTeq). The available evidence from clinical trials suggests co-administration of oral rotavirus vaccines is safe and effective and does not interfere with the immune response to the other vaccine antigens (DTPa, Hib, IPV, hepB, and 7vPCV).^{28,29,35}

Recommendations

(i) Routine infant vaccination (*Safety-Grade B*)/(*Efficacy-Grade B*)/(*Immunogenicity-not assessed*)²⁷

Administration of a course of oral rotavirus vaccination is recommended for all infants in the first half of the first year of life. Vaccination of older infants and children is not recommended as there are theoretical concerns regarding use in older age groups (see 'Adverse events' below). Vaccination should occur at either 2 and 4 months of age (Rotarix), or 2, 4 and 6 months of age (RotaTeq), according to the following schedules (see also Table 3.18.1):

- **Rotarix** (human monovalent rotavirus vaccine)

The vaccination course of Rotarix consists of 2 doses at approximately 2 and 4 months of age. The first dose should be given between 6 and 14 weeks of age, and the second dose should be given by the end of the 24th week of age (6 months). The interval between the 2 doses should not be less than 4 weeks.

- **RotaTeq** (pentavalent human-bovine reassortant rotavirus vaccine)

The vaccination course of RotaTeq consists of 3 doses at approximately 2, 4, and 6 months of age. The first dose should be given between 6 and 12 weeks of age,

and all doses should be given by the end of the 32nd week of age (~7.5 months). The interval between doses should be 4 to 10 weeks.

Table 3.18.1: Age limits for dosing of oral rotavirus vaccines

	Doses	Age of routine oral administration	Age limits for dosing			Minimum interval between doses
			1st dose	2nd dose	3rd dose	
Rotarix (GlaxoSmithKline)	2 oral doses (1 mL/dose)	2 and 4 months	6–14 [†] weeks	10–24 [†] weeks	None	4 weeks
RotaTeq (CSL Biotherapies/Merck & Co Inc)	3 oral doses (2 mL/dose)	2, 4 and 6 months	6–12 [†] weeks	10–32 [†] weeks	14–32 [†] weeks	4 weeks

* The upper age limit for receipt of the first dose of Rotarix is 14.9 weeks, that is up to the anniversary of the 15th week of age and the upper age limit for receipt of the second dose of Rotarix is 24.9 weeks, that is up to the anniversary of the 25th week of age.

† The upper age limit for receipt of the first dose of RotaTeq is 12.9 weeks, that is up to the anniversary of the 13th week of age. The second dose of vaccine should preferably be given by 28 weeks of age to allow for a minimum interval of 4 weeks before receipt of the third dose, and the upper age limit for either the second or third doses is 32.9 weeks, that is by the anniversary of the 33rd week of age.

For infants in whom the first dose of rotavirus vaccine is inadvertently administered at an age greater than the suggested cut-off (14 weeks for Rotarix or 12 weeks for RotaTeq), the remaining vaccine doses should be administered as per the schedule, providing the minimum interval between doses can be maintained, and the course completed within the recommended age limits. The timing of the first dose should not affect the safety and efficacy of the second and third dose.⁷ Infants who develop rotavirus gastroenteritis before receiving the full course of rotavirus vaccinations should still complete the full 2- or 3-dose schedule (dependent on the brand of vaccine) because one rotavirus infection only provides partial immunity.⁷

(ii) Catch-up (no studies)

Routine ‘catch-up’ or primary vaccination of older children is *not* recommended. Infants should commence the course of rotavirus vaccination within the recommended age limits for the first dose. It is also necessary to ensure that doses are not given beyond the upper age limits for the final dose of the vaccine course (see (i) above). This is based on theoretical concerns regarding possible adverse events in older age groups (see ‘Adverse events’ below), and because the safety of rotavirus vaccination in older infants and children has not been established.

(iii) Premature infants (*Safety-Grade C*)
(*Efficacy-Grade C*)(*Immunogenicity-not assessed*)²⁷

Vaccination of preterm infants using either available rotavirus vaccine is indicated at a chronologic age of at least 6 weeks if clinically stable. Premature infants (<37 weeks' gestation) appear to be at increased risk of hospitalisation from viral gastroenteritis.³⁶ In clinical trials, RotaTeq or placebo was administered to 2070 preterm infants (25–36 weeks' gestational age; median 34 weeks) who experienced rates of adverse events after vaccination similar to matched placebo recipients.^{7,27} Efficacy against rotavirus gastroenteritis of any severity was evaluated in only a small subset of premature infants and appeared comparable to efficacy in term infants (70%; 95% CI: -15%–95%). These conclusions would also be expected to apply to Rotarix vaccine. If standard infection control precautions are maintained, administration of rotavirus vaccine to hospitalised infants, including hospitalised premature infants, would be expected to carry a low risk for transmission of vaccine viruses (see 'Precautions' below).

Contraindications

The only absolute contraindications to rotavirus vaccines are:

- anaphylaxis following a previous dose of either rotavirus vaccine, or
- anaphylaxis following any vaccine component.

Precautions

(i) Acute gastroenteritis

Infants with moderate to severe acute gastroenteritis should not be vaccinated until after recovery from their acute illness. Infants with mild gastroenteritis (including mild diarrhoea) can be vaccinated. The use of rotavirus vaccines has not been studied in infants with acute gastroenteritis.

(ii) Moderate to severe illness

As with other vaccines, infants with a moderate to severe illness should be vaccinated after recovery. In addition to the factors mentioned above in (i), this avoids superimposing potential adverse events related to vaccination with the concurrent illness.

(iii) Underlying conditions predisposing to severe rotavirus gastroenteritis

Conditions predisposing to severe or complicated rotavirus gastroenteritis include metabolic disorders or chronic gastrointestinal disease, such as Hirschsprung's disease, malabsorption syndromes or short gut syndrome.¹ Although the safety and efficacy of rotavirus vaccines have not been studied in such infants, because they are at greater risk of serious rotavirus disease over an extended age range, the potential benefits of vaccination at an age older than the upper limits recommended in Table 3.18.1 are likely to be substantial. Vaccination of such children at an older age may be judged by clinicians to warrant

discussion with parents on a case by case basis (see 'Variations from product information' below).

(iv) Infants with impaired immunity

There are no studies of the safety or efficacy of the currently available rotavirus vaccines in infants with impaired immunity. As with other live viral vaccines, there are theoretical concerns that vaccine virus-associated gastrointestinal disease could occur in infants with severely impaired immunity who receive rotavirus vaccines. However, the theoretical risk for vaccine virus-associated disease in immune-impaired vaccinated infants is likely to be less than their risk from being exposed to disease from natural infection. Risks and benefits of vaccination should be considered in the context of the infant's specific immune impairment with appropriate specialist advice⁷ (see (v) below, and Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*).

(v) Infants living in households with people with impaired immunity

Infants living in households with people who have impaired immunity should be vaccinated. In general, household members with impaired immunity are afforded protection by vaccination of young children in the household. This outweighs the small risk for transmitting vaccine virus shed in stool to the household member with impaired immunity. The theoretical risk for vaccine virus-associated disease in contacts with impaired immunity is considered less than their risk of being exposed to disease from natural infection. However, there have been no studies to specifically address this question.⁷ (See also Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*.)

(vi) Recent administration of antibody-containing blood products

Infants who have recently received antibody-containing blood products and are at an eligible age should be vaccinated. The interval between vaccination and receipt of the blood product should be as long as possible, but without delaying administration of vaccine beyond the suggested age limits for dosing (as per Table 3.18.1 above). This recommendation for maximising the interval is based on theoretical concern that passively acquired antibody to rotavirus may interfere with vaccine immunogenicity.⁷

(vii) Hospitalised infants

If a recently vaccinated child is hospitalised for any reason, no precautions other than routine standard precautions need be taken to prevent the spread of vaccine virus in the hospital setting. Administration of rotavirus vaccine to hospitalised infants, including hospitalised premature infants, is likely to carry a low risk for transmission of vaccine viruses if standard infection control precautions are maintained (see 'Vaccines' above).

(viii) Exposure of pregnant women to vaccinated infants

Infants living in households of pregnant women can receive rotavirus vaccines. Most pregnant women will have pre-existing immunity to rotavirus but avoidance of wild-type infection through the vaccination of infant contacts may benefit adults, including pregnant women, and outweighs any theoretical concern regarding exposure to vaccine viruses.

(ix) Regurgitation of vaccine dose

Readministration of the vaccine is not necessary after regurgitation, spitting out, or vomiting of a rotavirus vaccine. This is because there are limited data available on the safety of administering higher than the recommended dose of rotavirus vaccines. There are no studies of the efficacy of a partially administered dose(s).

Adverse events

(i) Intussusception (IS)

Current evidence indicates that intussusception (IS, a form of bowel obstruction) is not associated with either Rotarix or RotaTeq vaccines, especially when given to infants within the age limits studied in clinical trials.^{27,30,32} Post-licensure data in larger numbers of children will monitor if there is an increased risk of IS following rotavirus vaccination, particularly among those inadvertently receiving doses outside the recommended age limits. Concern about association between IS and rotavirus vaccines arose because a tetravalent rhesus-reassortant vaccine, called RotaShield, licensed in the United States (but not elsewhere) in 1998–99, was associated with IS in approximately 1 in 10 000 vaccine recipients.³⁷ The greatest risk of IS occurred within 3 to 14 days after the first dose, with a smaller risk after the second dose.^{37,38}

There is evidence that when the first dose of RotaShield was given at >3 months of age, the risk of intussusception was increased.³⁸ The pathogenesis of RotaShield-associated intussusception has not been determined. However, the current rotavirus vaccines (RotaTeq and Rotarix) differ in composition to RotaShield, which was also more reactogenic.^{39–41} The large-scale safety studies of the 2 current rotavirus vaccines included approximately 140 000 infants, and found the risk of IS in vaccine recipients to be similar to that of placebo recipients, and less than that estimated for RotaShield.^{27,30,32} To minimise background rates of IS, the clinical trials of Rotarix and RotaTeq limited administration of the first dose of vaccine to infants under 14 and 12 weeks of age, respectively, and did not give subsequent doses to infants beyond a certain age (24 weeks for Rotarix and 32 weeks for RotaTeq).^{27,30,32} As such, data on safety of these vaccines in older infants is not currently available (see ‘Recommendations’ above).

(ii) Other adverse events

Vaccine recipients developed gastrointestinal symptoms such as diarrhoea or vomiting in the week after rotavirus vaccination more commonly than placebo recipients (increased risk of up to 3%).^{27,30,32} Fever was not significantly more common in rotavirus vaccine recipients compared with placebo recipients in clinical trials of both available vaccines.^{27,30,32}

Interchangeability of rotavirus vaccines

Completion of a course of rotavirus vaccine should be with vaccine from the same manufacturer whenever possible. There are no studies that address the interchangeability of the 2 available rotavirus vaccines. However, if either dose 1 or 2 of vaccine is given as RotaTeq, a third dose of either rotavirus vaccine should be given, provided that the upper age limit and inter-vaccine interval, as defined above in 'Recommendations', Table 3.18.1, are met.

Variations from product information

The product information for Rotarix states that the vaccine should not be administered to subjects with chronic gastrointestinal disease. NHMRC recommends that pre-existing chronic gastrointestinal disease is not considered to be a contraindication to rotavirus vaccination (see 'Precautions' above).

References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.